The Crystal Structure of Respiratory Complex II

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Our mitochondria require oxygen to help produce a chemical called ATP, which can store chemical energy for later use. What makes the production of ATP possible? As we digest the food we eat, electrons are extracted from the chemical compounds that make up the food, and used to reduce oxygen. The favorable process of oxygen reduction is indirectly coupled to the unfavorable process of ATP synthesis by a set of five protein complexes, numbered I - V, that bridge the mitochondrial membrane (Fig. 1).

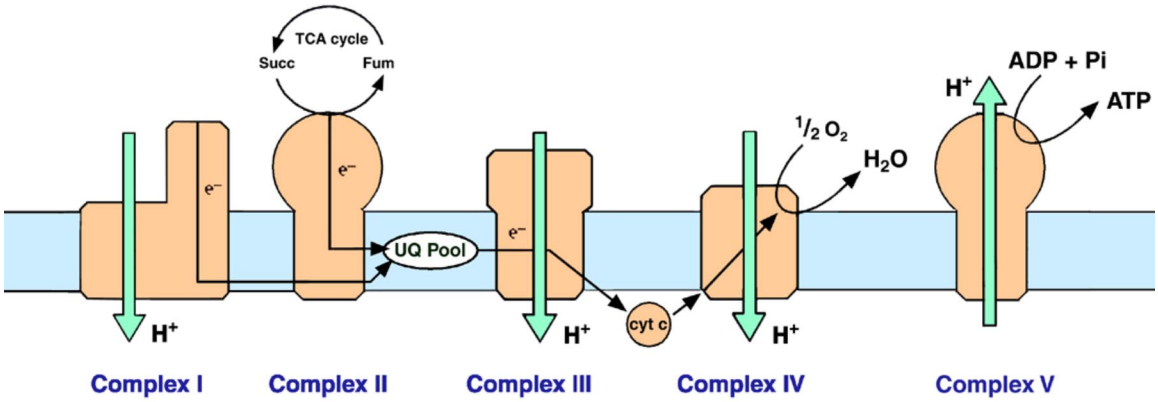

Fig. 1 Schematic representation of the aerobic respiratory chain. Complexes I-V are labeled and the pathway of electron transfer is indicated.

However, some organisms, like the bacteria found in our digestive tracts, don't require oxygen for ATP synthesis, and instead can utilize the chemical fumarate ($C_4H_2O_4^{2-}$) in the place of oxygen. Fumarate is normally a byproduct of aerobic respiration. By reversing the direction of one reaction, and reducing fumarate, ATP synthesis can proceed in the absence of oxygen. The reaction that is affected is catalyzed by a protein complex called Complex II. As Complex II is involved in such a fundamental metabolic process, genetic mutations are often embryonic lethal. In the cases where mutations are not lethal, they cause severe symptoms similar to those seen in multiple sclerosis. Although Complex II has been extensively studied, there are still many mysteries as to how it functions. Understanding the mechanism of how proteins function requires knowledge of their structures.

X-rays generated at the ALS beamline 5.0.2 were used to determine the structure of Complex II from the common bacterium *Eschericia coli*. The use of beamline 5.0.2 was critical for several reasons. First, it allowed a tunable wavelength, where most x-ray crystallography beamlines do not, which was important for determining structural information for complex II through the use of the anomalous scattering effect at the Fe K edge. Second, the ALS beamline 5.0.2 has a higher intensity than many other protein crystallography beamlines, and therefore allowed a higher signal in the diffraction data.

The structure of Complex II revealed an essentially modular enzyme with two independently folded soluble domains and two transmembrane anchors (Fig. 2). The active site of the enzyme is located in the flavoprotein subunit (Fig. 2, blue domain) near a cofactor called a flavin. The understanding of the chemical composition of the amino acid residues and cofactors located near where the reaction takes place allows us to better understand the mechanism of biological oxidation and reduction catalyzed by Complex II. By looking at the cofactors attached to the protein chain (Fig. 3), it is apparent how electrons can be transferred away from the food molecule bound at the active site of the enzyme and into the membrane where they can interact with Complex III (Fig. 1). This structure gives us insight into how both aerobic respiration occurs in humans as well as how anaerobic respiration occurs in other organisms.

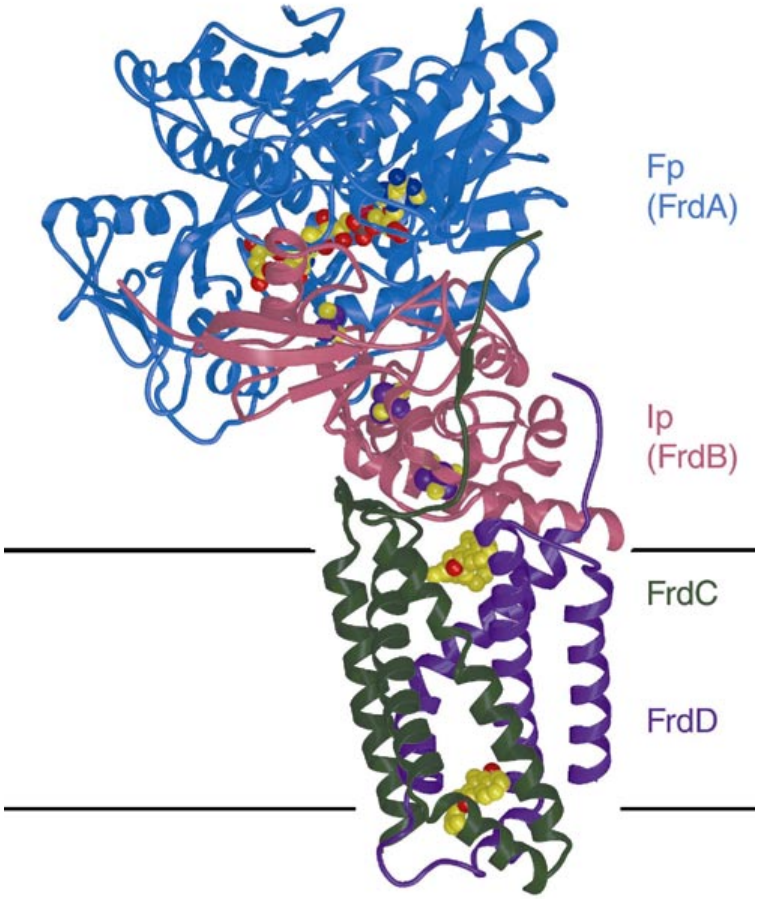

Fig. 2 High resolution structure of Complex II. The figure was produced by drawing a line through the polypeptide chain of the protein. The flavoprotein subunit is colored blue, the iron protein is colored pink, and the two membrane anchors are green and purple. Black lines show where the boundaries of the membrane might be located.

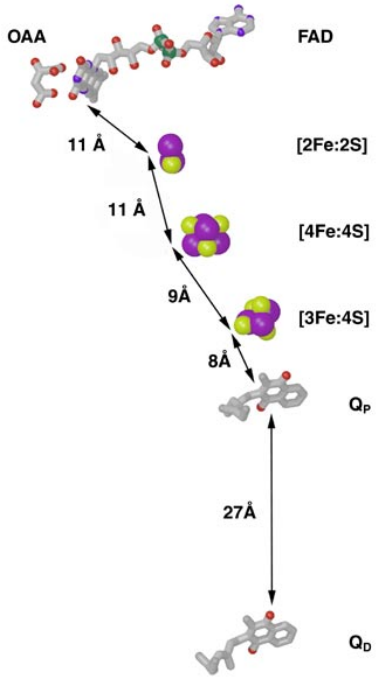

Fig. 3 Cofactors involved in electron transfer in Complex II. The figure is in the same view as Fig. 2, but with the protein stripped away. The distances shown are the closest distances between each redox cofactor. An electron likely follows the linear pathway along the arrows.

REFERENCES

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